CANADA COMMUNICABLE DISEASE REPORT

# CCDR

40 years! (1975-2015)

October 1, 2015 • VOLUME 41•10
ISSN 1481–8531

## Inside this issue: Vaccines

There are a lot of good developments in the area of vaccines. Know the latest recommendations for influenza vaccines this season, including the use of quadrivalent vaccines, especially in infants and young children. Learn about the re-emergence of polio, and why acute flaccid paralysis surveillance here in Canada remains critical. And for something completely different, read about some recent cases of Q fever that arose from medical tourism and live cell therapy.

---

### Rapid Communication

Q fever outbreak among travelers to Germany associated with live cell therapy — United States and Canada, 2014: a co-publication .....222
Robyn MP, Newman AP, Amato M, Walawander M, Kothe C, Nerone JD et al

### Advisory Committee Statement

Summary of the National Advisory Committee on Immunization (NACI) Statement on Seasonal Influenza Vaccine for 2015-2016.....226
Gemmill I on behalf of the National Advisory Committee on Immunization (NACI)

### Commentary

The polio eradication endgame: Why immunization and continued surveillance is critical..... .....232
Booth TF, Grudeski E, McDermid A, Rotondo J

### Evaluation

A spot of bother: Why varicella vaccine programs matter.....240
Harris T, Seo YC, Shing E, Wong K, Fediurek J, Deeks SL

### ID News

Innovations in vaccine development and surveillance.....249

### Useful resources

Immunize Canada. **Influenza Immunization Awareness Campaign**: 2015-2016 Campaign resources http://immunize.ca/en/events/influenza-imm-campaign.aspx

### Upcoming conferences

**November 11-13, 2015:** European Centre for Disease Control. **European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE)**: Stockholm, Sweden
http://ecdc.europa.eu/en/escaide/Pages/ESCAIDE.aspx

**November 12-14, 2015:** College of Family Physicians of Canada. **Family Medicine Forum**: Toronto, ON
http://fmf.cfpc.ca/

---

Public Health Agency of Canada | Agence de la santé publique du Canada

Canada

# Canada Communicable Disease Report

The *Canada Communicable Disease Report* (CCDR) is a bilingual, peer-reviewed, open-access online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public-health professionals, and policy-makers to inform policy, program development and practice.


**Editorial Office**

Patricia Huston, MD, MPH
Editor-in-Chief

Mylène Poulin, BSc, BA
A/Managing Editor

Wendy Patterson
A/Production Editor
613-884-3361

Diane Staynor
Editorial Assistant
613-851-5033

Diane Finkle-Perazzo
Cathy Robinson
Jane Coghlan
Lise Lévesque
Copy Editors

**CCDR Editorial Board**

Michel Deilgat, CD, BA, MD, CCPE
Centre for Foodborne, Environmental and Zoonotic Infectious Diseases
Public Health Agency of Canada

Catherine Dickson, MDCM, MSc
Resident, Public Health and Preventive Medicine, University of Ottawa

Jennifer Geduld, MHSc
Centre for Foodborne, Environmental and Zoonotic Infectious Diseases
Public Health Agency of Canada

Judy Greig, RN, BSc, MSc
Laboratory for Foodborne Zoonoses
Public Health Agency of Canada

Judy Inglis, BSc, MLS
Office of the Chief Science Officer
Public Health Agency of Canada

Maurica Maher, MSc, MD, FRCPC
National Defence

Mohamed A. Karmali, MB ChB, FRCPC
Infectious Disease Prevention and Control Branch
Public Health Agency of Canada

Julie McGihon
Public Health Strategic Communications Directorate
Public Health Agency of Canada

Robert Pless, MD, MSc
Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada

Hilary Robinson, MB ChB, MSc, FRCPC
Health Security Infrastructure Branch
Public Health Agency of Canada

Rob Stirling, MD, MSc, MHSc, FRCPC
Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada

Jun Wu, PhD
Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada



Canada Communicable Disease Report
Public Health Agency of Canada
130 Colonnade Rd.
Address Locator 6503B
Ottawa, Ontario K1A 0K9
Email: CCDR-RMTC@phac-aspc.gc.ca

To promote and protect the health of Canadians through leadership, partnership, innovation and action in public health.
Public Health Agency of Canada

Published by authority of the Minister of Health.


© Her Majesty the Queen in Right of Canada, represented by the Minister of Health, 2015


ISSN 1481-8531
Pub.150005

This publication is also available online at http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/15vol41/index-eng.php
Également disponible en français sous le titre: *Relevé des maladies transmissibles au Canada*

Rapid Communications

# Q fever outbreak among travelers to Germany associated with live cell therapy — United States and Canada, 2014: a co-publication†

**Robyn MP[1,2*], Newman AP[2], Amato M[3], Walawander M[3], Kothe C[4], Nerone JD[4], Pomerantz C[4], Behravesh CB[5], Biggs HM[1,5], Dahlgren FS[5], Pieracci EG[1,5], Whitfield Y[6], Sider D[6], Ozaldin O[7]; Berger L[7]; Buck PA[8], Downing M[9,10], Blog D[2]**

[1]Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, GA
[2]New York State Department of Health, Albany, NY
[3]Erie County Department of Health, Buffalo, NY
[4]Ulster County Department of Health and Mental Health, Ellenville, NY
[5]National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA;
[6]Public Health Ontario, Toronto, ON
[7]Toronto Public Health, Toronto, ON
[8]Centre for Food-borne, Environmental and Zoonotic Infectious Diseases, Public Health Agency of Canada, Ottawa, ON
[9]Saint Joseph's Health Centre, Toronto, ON
[10]Department of Medicine, University of Toronto, Toronto, ON

†This paper is identical in content to the primary article published in the *Morbidity and Mortality Weekly Report (MMWR)* and released electronically on September 30, 2015 having met the guidelines for simultaneous publication as set forth by the International Committee of Medical Journal Editors (www.icmje.org).

*Correspondence: mrobyn@cdc.gov

## Summary

**What is already known on this topic?**
Q fever is a zoonotic disease caused by *Coxiella burnetii* and is usually transmitted through inhalation of air contaminated with animal excreta. The disease is considered to be underdiagnosed because symptoms are nonspecific and can vary from patient to patient, making diagnosis difficult.

**What is added by this report?**
During September–October 2014, the New York State Department of Health identified Q fever in five patients with exposure to a treatment known as live cell therapy, an alternative medicine practice involving injections of fetal sheep cells, which is a type of xenotransplantation. Investigation revealed that a group of U.S. residents traveled to Germany twice a year to receive this treatment.

**What are the implications for public health practice?**
Clinicians should consider zoonotic diseases, such as Q fever, in patients whose history includes receipt of a treatment known as live cell therapy. International travel for xenotransplantation procedures can facilitate transmission of zoonotic disease.

## Introduction

During September–November 2014, the New York State Department of Health (NYSDOH) was notified of five New York state residents who had tested seropositive for *Coxiella burnetii*, the causative agent of Q fever. All five patients had symptoms compatible with Q fever (e.g., fever, fatigue, chills, and headache) and a history of travel to Germany to receive a medical treatment called "live cell therapy" (sometimes called "fresh cell therapy") in May 2014. Live cell therapy is the practice of injecting processed cells from organs or fetuses of nonhuman animals (e.g., sheep) into human recipients (1). It is advertised to treat a variety of health conditions. This practice is unavailable in the United States; however, persons can travel to foreign

locations to receive injections. Local health departments interviewed the patients, and NYSDOH notified CDC and posted a report on CDC's Epidemic Information Exchange to solicit additional cases. Clinical and exposure information for each patient was reported to the Robert Koch Institute in Germany, which forwarded the information to local health authorities. A Canada resident who also received live cell therapy in May 2014 was diagnosed with Q fever in July 2014. Clinicians should be aware of health risks, such as Q fever and other zoonotic diseases, among patients with a history of receiving treatment with live cell therapy products.

The five New York patients had traveled in a group of 10–15 persons to the state of Rhineland-Palatinate in Germany to receive intramuscular injections of fetal sheep cells from a German physician on May 30, 2014. A Canada resident, who received intramuscular injections of fetal sheep cells from the same German physician on May 28, 2014, sought medical care in June 2014 for fever, pain, and erythema at the site of the injection. She received a diagnosis of Q fever in July 2014, and public health authorities were notified. Under International Health Regulations, the Public Health Agency of Canada notified German authorities in September 2014. At the time of notification, the ministry of health of the federal state of Rhineland-Palatinate was investigating an outbreak of human Q fever associated with inhalation exposure to a sheep flock that was used for production of fetal sheep cell injections by the German physician.

In September, the German physician notified patients treated during January–July 2014 of their potential Q fever exposure. This prompted Q fever testing of the five patients in New York, three of whom had already sought medical care for symptoms. The other two patients had experienced symptoms but had not sought medical care until notification of their potential Q fever exposure. The test results, with positive Q fever titers, were reported to NYSDOH and prompted investigation by local health departments. No additional U.S. or Canada residents with positive Q fever titers and history of intramuscular injections of fetal sheep cells in Germany have been identified. The identities and nationalities of the other persons in the travel group are unknown to U.S. and Canadian public health authorities. It is not known whether the other persons did not get tested for Q fever, tested negative, or did not report an exposure to fetal sheep cell injections.

An outbreak-associated case of Q fever was defined as an illness consisting of clinical signs and symptoms compatible with Q fever, and a single IgG titer ≥1:128 to *C. burnetii* phase II antigen by immunofluorescence assay in a person who received live cell therapy in Germany during May 2014 (2). Among the six identified cases, the median patient age was 62 years (range = 59–83 years). Four of the six patients were female. None of the patients reported other potential exposures to Q fever, with the exception of one patient who reported contact with sheep horn or bone. Three patients reported preexisting medical conditions: one patient with atrial fibrillation and kidney stones, one patient with Parkinson disease and osteoarthritis, and one patient with multiple sclerosis.

Signs and symptoms of Q fever began within approximately 1 week of receipt of the intramuscular injections of fetal sheep cells. The majority of symptoms were reported as lasting approximately 10–90 days; however, 9–10 months after exposure, three patients continued to report symptoms of fatigue, chills, sweats, and difficulty sleeping (Table). One patient had initially reported no symptoms during an interview with the local health department after his positive titers were reported in November 2014; however, in February 2015, he informed his physician that symptoms had been occurring since the injections in May.

The patients were tested for Q fever phase I and phase II antibodies at 2–6 months after exposure, using indirect immunofluorescence assay. *C. burnetii* undergoes antigenic phase variation, between a virulent phase I form and an avirulent phase II form. During acute infection, phase II antibodies appear first and are higher than phase I antibodies. All patients' phase I IgG titers were elevated (1:512–1:2,048), but were lower than phase II IgG titers (1:4,096–1:65,536), suggesting acute disease. Phase I IgM titers were elevated in four patients (1:128–1:8,192) and phase II IgM titers were elevated in all patients (1:64–1:32,768). All patients were treated with doxycycline after receiving a diagnosis of Q fever.

All six patients were initially interviewed by their local health departments; only two of the five New York patients agreed to a follow-up interview by NYSDOH. The two patients reported that a group had traveled to Germany for injections twice each year for the past 5 years. They chose to receive injections of fetal sheep cells to improve their general health and vitality, and had not previously experienced signs or symptoms of

illness after injections. They reported that they were not informed of a risk for Q fever infection before injection.

**TABLE. Signs and symptoms reported by six Q fever patients who underwent live cell therapy — United States and Canada, 2014**

| Sign/Symptom | Patient 1 | Patient 2* | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| Fever | X | | X | X | X | X |
| Sweats | X | | X | X | X | |
| Fatigue | X | X | | X | X | X |
| Headache | X | | X | | X | |
| Chills | X | X | X | | | |
| Malaise | | | X | X | X | |
| Cellulitis | | | X | | X | X |
| Confusion | X | | | | | |
| Retrobulbar pain | X | | | | | |
| Injection site abscess | | | X | | | |
| Cough | | | X | | | |
| Dizziness | | | X | | | |
| Shortness of breath | | | X | | | X |
| Sore throat | | | X | | | |
| Dry mouth | | | X | | | |
| Diarrhea | | | X | | | |
| Difficulty sleeping | | | | X | | |
| Joint pain | | | | | X | |
| Myalgia | | | | | X | |
| Duration | 10–30 days | 9 months (fatigue and chills were ongoing as of February 2015) | 2–3 months | 14–30 days (fatigue and difficulty sleeping were ongoing as of February 2015) | 30 days (fatigue and sweats were ongoing as of February 2015) | 10 days (fatigue continued for several months) |

*Patient 2 initially reported no symptoms.

## Discussion

The treatment known as live cell therapy was developed in Switzerland during the 1930s by Paul Niehans. Practitioners have used organs, glands, and fetuses of multiple species, including sheep, cows, and sharks.* (1).

No published clinical evidence supporting therapeutic claims of the treatment known as live cell therapy is available. It is advertised as having anti-aging effects and as a treatment for multiple conditions and diseases (e.g., erectile dysfunction, depression, and joint, neurologic, heart, kidney, lung, endocrine, and liver disease).† Serious adverse events have been reported, including anaphylaxis, vasculitis, encephalitis, polyradiculitis, clostridial infections, paresis, and death (3–5).

The treatment known as live cell therapy is a type of xenotransplantation when it involves administration of live cells from a nonhuman animal source into a human recipient (6). Xenotransplantation carries a public health risk for transmission of known and unknown infectious agents from the donor organism to the human recipient and possible recombination or reassortment to form new pathogens (6). There is a theoretic potential for dissemination of disease from the original recipient to others. For this reason, discussions on safety requirements for xenotransplantation by international and domestic public health agencies continue to occur (7).

Regulation of xenotransplantation varies among countries. In the United States, the Food and Drug Administration (FDA) regulates xenotransplantation products as Biologic Drugs under section 351 of the Public Health Service Act§ and the Federal Food, Drug, and Cosmetic Act.¶ FDA approval of a Biologics License Application (BLA) is required to introduce, or deliver for introduction, a biologic product into interstate commerce. FDA has not approved a BLA for a xenotransplantation product known as live cell

therapy. If a xenotransplantation product is proposed for use in a clinical investigation in the United States, an Investigational New Drug Application would be required. In Canada, xenotransplantation cell therapy products are regulated as drugs under the Food and Drugs Act[**] and the Food and Drug Regulations.[††] Authorities in Canada have not authorized for sale any xenotransplantation products, nor have any clinical trials that involve xenotransplantation been authorized. In Germany, xenotransplantation products are regulated under the Medicinal Products Act; however, an attempt to ban fresh cell therapy in 1997 was later determined to be null and void because the federal law does not cover drugs manufactured by doctors only for use in their own patients (8). According to an assessment supported by the World Health Organization and its partners, during January 1994–September 2009, xenotransplantation procedures were identified in 12 different countries, of which nine had no clear national regulations on xenotransplantation (9).

This outbreak highlights one of the public health issues associated with xenotourism, the travel outside a country of residence for the purpose of participating in xenotransplantation programs. FDA recommends that xenotransplantation product recipients enrolled in research studies remain under lifelong surveillance with periodic clinical and laboratory monitoring and that both they and their intimate contacts refrain from blood and tissue donation (6). However, other than self-reporting, no method to identify returned xenotourists is available. Clinicians should be aware of xenotourism and consider the potential for zoonotic disease in a patient with a history of xenotransplantation.

## Acknowledgments

Stephen Moore, Ryan Walton, Bryna Warshawsky, MD, Public Health Ontario. Samir N Patel, PhD, Public Health Ontario and University of Toronto. Maja George, PhD, Robert Koch Institute and European Centre for Disease Prevention and Control. Ann Sullivan-Frohm, Christina Hidalgo, MPH, Philip Kurpiel, PhD, New York State Department of Health. Canada IHR National Focal Point Office, Public Health Agency of Canada.

## References

(1) U.S. Congress, Office of Technology Assessment, Unconventional Cancer Treatments, OTA-H-405. Washington, DC: U.S. Government Printing Office; September 1990.

(2) Centers for Disease Control and Prevention. Notes from the field: Q fever outbreak associated with goat farms—Washington and Montana, 2011. Morb Mortal Wkly Rep 2011;60;1393.

(3) Bohl J, Goebel HH, Potsch L, Esinger W, Walther G, Mattern R, et al. Complications following cell therapy. Zeitschrift fur Rechtsmedizin 1989;103:1–20.

(4) Goebel HH, Walther G, Meuth M. Fresh cell therapy followed by fatal coma. J Neurol 1986;233:242–7.

(5) The Lancet. Cell therapy suspended. Lancet. 1987; 330(8557):503.

(6) Guidance for Industry: Source animal, product, preclinical, and clinical issues concerning the use of xenotransplantation products in humans. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics and Research; 2003 April. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm074354.htm.

(7) World Health Organization. Second WHO Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials. Geneva, Switzerland; October 17-19, 2011. http://www.who.int/transplantation/xeno/report2nd_global_consultation_xtx.pdf?ua=1.

(8) Federal Constitutional Court. Ban on fresh cell production is void. Bund has no regulatory powers. Press release No. 18/2000; February 16, 2000 [German]. http://www.bundesverfassungsgericht.de/SharedDocs/Pressemitteilungen/DE/2000/bvg00-018.html.

(9) Sgroi A, Bühler LH, Morel P, Sykes M, Noel L. International human xenotransplantation inventory. Transplantation 2010;90:597–603.

* Additional information available at http://www.extendlife.com/livecell.php.
† Additional information available at http://www.janson-mueller.de/index.php?id=22&L=2.
§ 42 U.S.C. 262.
¶ 21 U.S.C. 321 et seq.
** R.S.C., 1985, c. F-27.
†† C.R.C., c. 870.

National Advisory Committee Statement

# Summary of the National Advisory Committee on Immunization (NACI) Statement on Seasonal Influenza Vaccine for 2015–2016

**Gemmill I[1, 2], on behalf of the National Advisory Committee on Immunization (NACI)**

[1] Chair, NACI
[2] Kingston, Frontenac and Lennox & Addington Public Health, Kingston, ON

Correspondence: NACI-CCNI@phac-aspc.gc.ca

## Abstract

**Background:** The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada with ongoing and timely medical, scientific, and public health advice relating to immunization.

**Objective:** To summarize the update of the 2015–2016 recommendations by NACI regarding the use of seasonal influenza vaccines.

**Methods:** Annual influenza vaccine recommendations are developed by the Influenza Working Group for consideration by NACI, based on NACI's evidence-based process for developing recommendations, and includes: a consideration of the burden of influenza illness and the target populations for vaccination; efficacy and effectiveness, immunogenicity, and safety of influenza vaccines; vaccine schedules; and other aspects of influenza immunization.

**Results:** NACI continues to recommend influenza vaccination for all individuals aged 6 months and older, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk, and others as indicated. For the 2015–2016 influenza season, the Statement has been updated to identify children and adolescents with neurologic or neurodevelopment conditions as a group at high risk for influenza-related complications or hospitalization. Several changes to product availability in Canada have also been noted. A new adjuvanted, trivalent influenza vaccine (Fluad Pediatric™ [Novartis]) will be available for use in children aged 6 to <24 months. The recommended choice of product for this age group, however, is quadrivalent inactivated influenza vaccine (QIV), because children are more likely to be affected by influenza B, and the QIV provides broader protection against both lineages of influenza B. If QIV is not available, either unadjuvanted or adjuvanted trivalent inactivated influenza vaccine (TIV) should be used. Only the quadrivalent formulation of the live attenuated influenza vaccine (LAIV) (FluMist® Quadrivalent [AstraZeneca]) will be available, and the recommendation for preferential use of LAIV in children 2 to 17 years of age who do not have contraindications to this vaccine remains unchanged following a review of information pertaining to reports of decreased effectiveness of LAIV in the United States during the 2013–2014 season. Finally, the intradermal trivalent influenza vaccine (Intanza® [Sanofi Pasteur]) will no longer be available for use in Canada. Other updates to the Statement include additional information reaffirming the safety of LAIV use in children with cystic fibrosis who are not considered immunosuppressed or receiving immunosuppressive treatment, as well as a revised definition for oculo-respiratory syndrome which, when it occurs, should be reported as an adverse event following immunization (AEFI) to local public health officials.

**Conclusion:** Vaccination is the safest, longest lasting and most effective way to prevent influenza.

## Introduction

Every year, the National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada with recommendations on seasonal influenza vaccines for the upcoming season as part of its mandate to develop evidence-based medical, scientific, and public health advice relating to immunization. NACI develops Advisory Committee statements on new vaccines and vaccine-related issues and maintains its evergreen edition of the *Canadian Immunization Guide* (1). The objective of this Statement is to summarize both the update of the *Canadian Immunization Guide* Chapter on Influenza and the *Statement of Seasonal Influenza Vaccine* for 2015–2016 (2).

## Methods

Annual influenza vaccine recommendations are developed by the Influenza Working Group (IWG) for consideration by NACI, based on NACI's evidence-based process for developing recommendations (3). This process includes: a consideration of the burden of influenza illness and the target populations for vaccination; data on efficacy and effectiveness, immunogenicity, and safety, of influenza vaccines; vaccine schedules; and other aspects of influenza immunization.

## Recommendations

NACI continues to recommend influenza vaccination for all individuals aged 6 months and older, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk, and others as indicated (**Table 1**). In particular, following a recent publication by the Canadian Immunization Monitoring Program ACTive (IMPACT) (4), NACI now includes children and adolescents with neurologic or neurodevelopment conditions (including seizure disorders, febrile seizures and isolated developmental delay) as a chronic health condition, and therefore among the groups for whom influenza vaccination is particularly recommended. Healthy individuals 5 to 64 years of age also benefit from influenza vaccination, as do travellers aged 6 months and older, since in the tropics influenza occurs year round; in temperate zones, influenza occurs from November to March in the northern hemisphere and April to October in the southern hemisphere.

**Table 1: NACI 2015–2016 recommendations for influenza vaccination[1]**

**People at high risk of influenza-related complications or hospitalization**

- Adults, including pregnant women, and children with the following chronic health conditions:
  - cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma)
  - diabetes mellitus and other metabolic diseases
  - cancer, immune compromising conditions (due to underlying disease, therapy or both)
  - renal disease
  - anemia or hemoglobinopathy
  - conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration
  - morbid obesity (BMI ≥40)
  - children and adolescents (aged 6 months to 18 years) with the following conditions:
    - *neurologic or neurodevelopment conditions (including seizure disorders, febrile seizures and isolated developmental delay)*
    - undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye's syndrome associated with influenza.
- People of any age who are residents of nursing homes and other chronic care facilities.
- People ≥65 years of age.

- All children 6 to 59 months of age.
- Healthy pregnant women (the risk of influenza-related hospitalization increases with length of gestation, i.e., it is higher in the third than in the second trimester).
- Aboriginal Peoples.

**People capable of transmitting influenza to those at high risk**

- Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk of influenza complications.
- Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunized):
  - household contacts of individuals at high risk, as listed in the section above
  - household contacts of infants <6 months of age as these infants are at high risk of complications from influenza but cannot receive influenza vaccine
  - members of a household expecting a newborn during the influenza season
- Those providing regular child care to children ≤59 months of age, whether in or out of the home.
- Those who provide services within closed or relatively closed settings to persons at high risk (e.g., crew on a ship).

**Others**

- People who provide essential community services.
- People in direct contact during culling operations with poultry infected with avian influenza.

[1] New recommendations are noted in italic.

### Children 6 to less than 24 months

For children 6 to 23 months of age NACI recommends that, given the burden of influenza B disease, quadrivalent inactivated influenza vaccine (QIV) should be used. If QIV is not available, either unadjuvanted or adjuvanted trivalent inactivated influenza vaccine (TIV) should be used. A new adjuvanted, trivalent influenza vaccine, Fluad Pediatric™ (Novartis), will be available on the Canadian market, starting in the 2015–2016 influenza season, for use in children aged 6 to <24 months and is administered as a 0.25 mL dose by intramuscular injection.

### Children and adolescents 2 to 17 years

NACI recommends live attenuated influenza vaccine (LAIV) use for healthy children and adolescents 2 to 17 years of age who do not have contraindications to this vaccine. Only the quadrivalent formulation of LAIV (FluMist® Quadrivalent [AstraZeneca]) will be available in Canada in the 2015–2016 season. The 2015–2016 Statement has been updated to reflect that the evidence supporting the use of live attenuated influenza vaccines was based on the trivalent formulation of LAIV. Based on expert opinion, the comparative efficacy data which supported the preferential recommendations for the trivalent formulation of LAIV are also applicable to the quadrivalent formulation of LAIV because the manufacturing processes and immunologic mechanism of the quadrivalent LAIV and the trivalent LAIV products are the same. This expert opinion is supported by the results of the non-inferiority studies comparing trivalent and quadrivalent formulations of LAIV, which were required by regulatory bodies to authorize the use of the quadrivalent LAIV formulation. Comparative vaccine efficacy and effectiveness data of TIV or QIV, and the quadrivalent formulation of LAIV are not available.

Decreased effectiveness of quadrivalent LAIV was seen in the United States against the influenza A (H1N1) strain during the 2013–2014 influenza season. Thermal stability tests have shown that the reduced stability likely resulted in strain degradation when experiencing deviations in temperature during storage or transport. Undocumented temperature deviations are unlikely to occur in Canada as, by contract, the manufacturer is required to maintain the required temperatures throughout transport to provincial and territorial depots.

Based on a review of available evidence, NACI continues to recommend preferential use of LAIV in children 2 to 17 years of age who do not have contraindications to this vaccine. NACI will continue to monitor this issue.

### All age groups

**Table 2** summarizes the choice of influenza vaccine for selected age and risk groups. **Table 3** identifies the recommended dosage and route of influenza vaccine for the 2015–2016 season, by age.

**Table 2: Choice of influenza vaccine for selected age and risk groups (for persons without a contraindication to the vaccine)**

| Recipient by age group | Vaccine types available for use[1] | Comments |
|---|---|---|
| **Children 6 to 23 months of age** | • TIV<br>• QIV<br>• Adjuvanted TIV | Given the burden of influenza B disease, QIV should be used. If QIV is not available, either unadjuvanted or adjuvanted TIV should be used. |
| **Children 2 to 17 years of age** | • TIV<br>• QIV<br>• LAIV | NACI recommends LAIV for healthy children and adolescents 2 to 17 years of age who do not have contraindications to this vaccine.<br>LAIV is contraindicated for: children less than 24 months of age, due to increased risk of wheezing; individuals with severe asthma[2]; children and adolescents <18 years of age who are receiving aspirin or aspirin-containing therapy; pregnant women; and persons with immune compromising conditions, due to underlying disease, therapy, or both.<br>LAIV, TIV or QIV can be used in children with chronic health conditions, including asthma that is not severe[2] and cystic fibrosis without immune suppression. |
| **Adults 18 to 59 years of age** | • TIV<br>• QIV<br>• LAIV | Any of these three vaccines may be used, unless contraindicated, for healthy adults in this age group.<br>TIV and QIV are the preferred products for adults with chronic health conditions.<br>LAIV is not recommended for adults with immune compromising conditions. |
| **Adults 60 to 64 years of age** | • TIV<br>• QIV | Either of these vaccines can be used, unless contraindicated, for adults in this age group. |
| **Adults ≥65 years of age** | • TIV<br>• QIV<br>• Adjuvanted TIV | Any of these three vaccines may be used, unless contraindicated, for healthy adults in this age group. |
| **Pregnant women** | • TIV<br>• QIV | LAIV is not recommended because of the theoretical risk to the fetus from administering a live virus vaccine. |

[1] TIV = trivalent inactivated influenza vaccine (for intramuscular [IM] administration); QIV = quadrivalent inactivated influenza vaccine; LAIV = live attenuated influenza vaccine

[2] An individual with severe asthma is defined as someone who is currently on oral or high dose inhaled glucocorticosteriods, is active wheezing, or has had medically attended wheezing in the seven days prior to vaccination.

**Table 3: Influenza vaccine: Recommended dosage and route, by age, for the 2015–2016 season**

| Age group | TIV[1,2] without adjuvant or QIV[1,2] IM[1] | MF59-adjuvanted TIV (Fluad Pediatric™ or Fluad®) IM | LAIV[1] (FluMist® Quadrivalent) IN | Number of doses required |
|---|---|---|---|---|
| **6 to 23 months** | 0.5 mL[3] | 0.25 mL | — | One or two[4] |
| **2 to 8 years** | 0.5 mL | — | 0.2 mL (0.1 mL per nostril) | One or two[4] |
| **9 to 17 years** | 0.5 mL | — | 0.2 mL (0.1 mL per nostril) | One |
| **18 to 59 years** | 0.5 mL | — | 0.2 mL (0.1 mL per nostril) | One |
| **60 to 64 years** | 0.5 mL | — | — | One |
| **≥65 years** | 0.5 mL | 0.5 mL | — | One |

[1] TIV = trivalent inactivated influenza vaccine; QIV = quadrivalent inactivated influenza vaccine; LAIV = live attenuated influenza vaccine; IM = intramuscular; IN = intranasal

[2] Influvac® ≥18 years; Fluviral® ≥6 months; Agriflu® ≥6 months; Vaxigrip® ≥6 months; Fluzone® ≥6 months; Flulaval® Tetra ≥6 months; and Fluzone® Quadrivalent ≥6 months.

[3] This information differs from the product monograph. As noted in the statement, recommendations for use and other information in this statement may differ from that set out in the product monographs/leaflets of the Canadian manufacturers (1).

[4] Children 6 months to less than 9 years of age who have never received the seasonal influenza vaccine, require two doses of influenza vaccine, with a minimum interval of four weeks between doses. Eligible children less than 9 years of age, who have properly received one or more doses of seasonal influenza vaccine in the past, should receive one dose per influenza vaccination season thereafter.

## Additional information

The target groups for influenza and pneumococcal polysaccharide vaccines overlap considerably. Health care providers should take the opportunity to vaccinate eligible persons against pneumococcal disease when influenza vaccine is given.

A Canadian study conducted during the 2012–2013 season followed a cohort of children and adolescents 2 to 18 years of age with cystic fibrosis, following administration of trivalent LAIV, to evaluate the safety of LAIV in this population (5). The vaccine was found to be well tolerated, and provided reassurance that LAIV is safe for use in this population. Children with cystic fibrosis may receive LAIV if the individual is not being treated with immunosuppressive drugs, such as prolonged systemic corticosteroids, and meets the other criteria for LAIV administration.

The definition for oculo-respiratory syndrome (ORS) has been updated. ORS is defined as the presence of bilateral red eyes plus one or more respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness or sore throat) that start within 24 hours of vaccination, with or without facial oedema. Few cases have been identified since the 2000–2001 influenza season. ORS is not considered to be an allergic response and, when it occurs, it should be reported as an adverse event following immunization (AEFI) to local public health officials.

Although, as a general rule, two live vaccines are given four weeks apart, there is no evidence that this interval is needed for live intranasal influenza vaccines and other live vaccines. Based on expert opinion, NACI recommends that LAIV can be given together with, or at any time before or after, the administration of any other live attenuated or inactivated vaccine.

Two recommendations from previous statements merit repetition. Immunization should not be delayed because of minor acute illness, with or without fever. If significant nasal congestion is present that might impede delivery of LAIV to the nasopharyngeal mucosa, inactivated vaccines can be administered or LAIV may be deferred until resolution of the illness. Egg allergic individuals may be vaccinated against influenza

using inactivated TIV or QIV, without prior influenza vaccine skin testing, and with the full dose, irrespective of a past severe reaction to egg, and without any particular consideration including immunization setting. As with all vaccine administration, however, immunizers should have the necessary equipment and be prepared to respond to a vaccine emergency at all times.

Finally, for the 2015–2016 influenza season, Intanza® will no longer be available on the Canadian market.

## Conclusion

Recommendations for influenza vaccination are updated annually as this field is in rapid development. Vaccination remains the safest, longest lasting and most effective way to prevent influenza.

## Acknowledgements

Many thanks to all the members of the Influenza Working Group and the National Advisory Committee on Immunization for their careful work and commitment to developing the 2015–2016 *Canadian Immunization Guide* Chapter on Influenza and *Statement on Seasonal Influenza Vaccine* for 2015–2016.

## Conflict of interest

None

## Funding

The National Advisory Committee on Immunization is funded by the Public Health Agency of Canada.

## References

(1) Public Health Agency of Canada. Canadian Immunization Guide. Updated 2015 May 20. http://www.phac-aspc.gc.ca/publicat/cig-gci/

(2) National Advisory Committee on Immunization. Statement on Seasonal Influenza Vaccine for 2015–2016. Public Health Agency of Canada. (Publication to follow)

(3) National Advisory Committee on Immunization. Evidence-based recommendations for immunization—Methods of the the National Advisory Committee on Immunization. CCDR. 2009 Jan; 35(ACS-1):1–10. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-1/index-eng.php

(4) Burton C, Vaudry W, Moore D, et al. Burden of seasonal influenza in children with neurodevelopmental conditions. Pediatr Infect Dis J. 2014;33(7):710–4.

(5) Boikos C, De Serres G, Lands LC, et al. Safety of live-attenuated influenza vaccination in cystic fibrosis. Pediatrics. 2014;134(4):e983–91.

Commentary

# The polio eradication endgame: Why immunization and continued surveillance is critical

**Booth TF[1,2]*, Grudeski E[1], McDermid A[1,2], Rotondo J[3]**

[1]Viral Diseases Division, National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB
[2]Department of Medical Microbiology, University of Manitoba, Winnipeg, MB
[3]Center for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada, Ottawa, ON

*Correspondence: tim.booth@phac-aspc.gc.ca

## Abstract

The poliovirus is very close to being eradicated from the world. To this end, the four main objectives of the World Health Organization's Polio Eradication & Endgame Strategic Plan 2013–2018 are to: detect and interrupt all poliovirus transmission; strengthen immunization systems and withdraw oral polio vaccine; contain poliovirus and certify interruption of transmission; and plan polio's legacy. There is a need to maintain vigilance for circulating vaccine-derived polioviruses as well as maintaining both epidemiological and laboratory surveillance for polio at this critical point in history. Despite the elimination of indigenous wild poliovirus transmission in Canada, the risk of wild poliovirus importation from endemic countries, and the risk of importation of circulating vaccine strains remains. Due to this ongoing risk, active surveillance of acute flaccid paralysis (AFP) in children less than 15 years of age remains important. At least one stool specimen from all suspect AFP cases should be sent to the National Microbiology Laboratory at the Public Health Agency of Canada for polio isolation and testing to support and verify Canada's polio-free status. An added benefit of this is that it may also help identify other non-polio enteroviruses, such as enterovirus D68.

## Introduction

Poliomyelitis is a highly infectious viral disease that can cause swift and irreversible paralysis, particularly in children. Since the introduction of polio vaccines in the 1950s, and the Global Polio Eradication Initiative in 1988, a strategy was developed to eliminate and to eventually eradicate poliovirus infection from the world, through the use of intensive and persistent immunization programs in every country. This vaccination strategy has been highly successful. The World Health Organization (WHO) has stated that, as a result of immunization, there are 10 million people walking today who would otherwise have been paralyzed (1). There have been recent setbacks, however, and in May 2014 the WHO declared the international spread of wild poliovius to be a "Public Health Emergency of International Concern" (2). As recently as September 2015, new cases of polio have been reported in Mali and the Ukraine (3).

The objective of this article is to: summarize the current situation; identify the recent challenges to the elimination strategy; identify new vaccine recommendations from the WHO; and highlight the importance of acute flaccid paralysis (AFP) surveillance around the world, including here in Canada.

### Polioviruses and the different vaccines

Poliovirus has three major strains or serotypes (PV1, PV2 and PV3) and is a member of the C group of enteroviruses in the picornavirus family, a diverse group of positive-stranded RNA viruses, which include many other non-polio enteroviruses (4). It is spread from person to person largely through the fecal-oral route. Approximately 90% of cases are asymptomatic, 10% have mild infection (fever, malaise, headache, nausea and vomiting), and less than 1% of cases develop an acute onset of flaccid paralysis that usually involve the lower limbs. When it involves respiratory muscles, it can be life-threatening (5).

There are two types of vaccine: oral polio vaccine (OPV) and injectable polio vaccine (IPV). Oral polio vaccine initially contained attenuated versions of all three strains, but PV2 will soon be omitted, due to the eradication of wild PV2. The injectable (inactivated) polio vaccine has drawbacks, including that it is more expensive, more difficult logistically to administer, and is less effective than the Sabin OPV. This is why OPV is still used in much of the world. The concern about OPV, however, is that its use can cause the circulation of vaccine-derived (specifically OPV-derived) polioviruses in populations. These vaccine-derived polioviruses often circulate asymptomatically in populations where oral polio vaccines are still used, and water sanitation is not optimal. These circulating OPV-derived polioviruses invariably revert, though mutation, to a form with increased neurovirulence. Infection by these viruses poses an increased risk of poliomyelitis, especially in persons that are immunocompromised or who have other underlying illnesses.

The resurgence of polio is not a high-profile issue in Canada, where IPV vaccine is used with recommended doses at 2, 4, 6 and 12 to 18 months of age, with a booster at 4 to 6 years of age. This is, however, a global problem and, in light of this, a single lifetime booster dose is now recommended for those at increased risk of exposure to polio (e.g., those travelling to, or planning to work in areas that have wild polio or vaccine-derived polio outbreaks) (6).

## Polio is re-emerging

A series of setbacks have occurred in the battle to rid the world of polio, resulting in polio spreading back into areas where it had been previously eliminated. To date, each time this has occurred, the outbreak has been contained through enhanced vaccination, but the battle is not yet over.

The outbreak in Tajikistan in 2010 (7) illustrates the complexity of eradicating the disease. Laboratory genetic analysis identified the causative agent as poliovirus 1 strain. The virus originated in India, and subsequently spread into the neighbouring countries of Kazakhstan, Russia, Turkmenistan and Uzbekistan. This large outbreak of poliomyelitis resulted in 463 laboratory-confirmed cases and 47 polio-compatible cases, and highlights the need for continued polio vaccination, polio campaigns and ongoing surveillance for polio, even in areas where vaccination rates are still high.

Despite these outbreaks due to imported viruses, the number of regions where wild polioviruses are endemic have steadily diminished. In 2012, there were only 223 polio cases identified worldwide, the fewest that have ever been recorded (8), and in 2013 polio was found to be endemic in only three countries—Afghanistan, Nigeria and Pakistan. By early 2014, polio was declared to have been eliminated from Southeast Asia, and in Africa was on the verge of elimination. It was apparent that the risk of outbreaks of paralytic disease arose from circulating vaccine-derived viruses from OPV—and had to be tackled.

In 2014, outbreaks began to occur in regions where polio had formerly been eliminated, including Cameroon, Equatorial Guinea, Ethiopia, Iraq, Israel, Somalia, and Syria (2).

In the Middle East, the outbreaks were caused by a poliovirus 1 strain that had spread from Pakistan. The WHO declared the international spread of wild poliovirus a Public Health Emergency of International Concern after documentation of numerous poliovirus exportations from polio-endemic countries (Pakistan, Afghanistan and Nigeria) to polio-free countries. Enhanced vaccination campaigns and travel requirements were introduced to control the spread of infection in these affected areas. See **Table 1** for a summary of the current global polio situation (2).

**Table 1:Revised designations* for infected states from the sixth meeting of the IHR Emergency Committee regarding the international spread of wild poliovirus.**

| Designation | States |
|---|---|
| States currently exporting wild poliovirus | Afghanistan, Pakistan |
| States no longer infected by wild poliovirus, but remain vulnerable to international spread | Nigeria, Somalia, Cameroon, Equatorial Guinea, Ethiopia, Iraq, Israel, Syria |

*As of September 24th, 2015.

### Children with poliovirus infections are still being diagnosed in Canada

Since 2005, there have been five importations of vaccine-strain poliovirus into Canada that were confirmed by the National Microbiology Laboratory (NML) of the Public Health Agency of Canada (**Appendix**). Four of these were incidental infections, in that the children were sampled for virological testing due to a non-paralytic illness and poliovirus was cultured from patient specimens. These individuals became infected with vaccine strains during travel to regions where oral vaccines were still in use, either by directly receiving the vaccine, or possibly becoming infected through environmental contamination. One case of vaccine-associated paralytic poliomyelitis was identified which was associated with a child that travelled to China on a vacation and received OPV while there, and presented with flaccid paralysis soon afterwards.

## The endgame strategy

To address the setbacks with polio, the WHO developed the Polio Eradication & Endgame Strategic Plan 2013–2018 that contains four main objectives: detect and interrupt all poliovirus transmission; strengthen immunization systems and withdraw oral polio vaccine; contain poliovirus and certify interruption of transmission; and plan polio's legacy (1). We will focus on the vaccine recommendations and the need for detection of all poliovirus transmission.

### Phasing out oral vaccine

In early 2014, the WHO recommended all countries use at least one dose of IPV (8). The reasoning for this is to prevent outbreaks of circulating OPV-derived polioviruses, which can result in cases of OPV-related poliomyelitis. Although IPV gives good humoral immunity and protection from poliomyelitis disease, it gives much less intestinal immunity. Thus, about 90% of children vaccinated with IPV are still prone to shedding the virus after being given OPV. Thus, the use of IPV alone would probably not be enough to eradicate circulating OPV-derived viruses. It has been shown that giving children a dose of IPV first, followed by booster of OPV, greatly reduced the shedding of OPV-derived virus in stool: the results were much better than giving a dose of OPV first and a second booster of OPV (9).

The WHO also recommended that OPV vaccine no longer include PV2 (10). This was based on data that showed wild polio PV2 is probably extinct (11) and wild PV3 has not been detected since 2012 (12). Removal of PV3 from OPV may follow the discontinuation of the PV2 component.

### Acute flaccid paralysis (AFP) surveillance

Surveillance for poliovirus relies on two things: the detection, reporting and stool testing of AFP in children or paralysis in any person who is suspected of being infected with poliomyelitis; and a laboratory that can positively identify poliovirus and distinguish wild polio from vaccine-derived disease. Nationwide AFP surveillance is the WHO gold standard for detecting cases of poliomyelitis (13).

As a member of the Global Poliovirus Laboratory Network, the NML is responsible for the virological testing of stool specimens from cases with a clinical suspicion of poliomyelitis. The WHO stipulates that stool samples from at least 80% of AFP cases in children less than 15 years of age should undergo virological

stool testing for poliovirus. Unfortunately, over the last decade or so, only about 30% of these cases have undergone laboratory testing, and very few of these tests were carried out by an accredited laboratory. This is the weak link in our current surveillance system.

To have a strong AFP surveillance system in Canada it is important to report cases of AFP in children under 15 years and submit stool specimens to the NML which is the only WHO-accredited laboratory for poliovirus testing in Canada. Details on how to submit specimens for testing at the NML are included below. This is important to do even when another plausible cause for the illness is found. For the diagnosis of poliovirus infection, virus culture from stool (in a special cell line that is highly sensitive to poliovirus) is still the most sensitive standard recommended by the WHO to identify polio. In addition, molecular testing, including reverse-transcription polymerase chain reaction testing to detect the viral genome, and genetic sequencing, is carried out to type and identify the origin of any polioviruses that are detected.

## What clinicians need to know

Acute flaccid paralysis (AFP) is defined as the acute onset of focal weakness or paralysis characterised as flaccid (reduced tone) without other obvious cause (e.g., trauma) in children less than 15 years old (14). AFP is nationally notifiable. Any attending physician who diagnoses AFP in children less than 15 years should report cases to the Canadian Pediatric Surveillance Program (CPSP) and to local public health in provinces and territories where AFP is notifiable by law (15). The CPSP has recently updated its AFP protocol and questionnaire (14). It is a best practice to arrange a 60-day follow up.

At least one stool sample needs to be collected within 14 days of the onset of paralysis and if more than one specimen is taken they should be 24-48 hours apart. No special medium is required; stool can be collected in any sterile leak-proof container. There should be at least 1 g and ideally 5 g to 10 g of stool for each sample. A cold chain is needed; samples need to be stored frozen at ≤-20°C and then shipped frozen on dry ice by those who are known to be compliant with Transportation of Dangerous Goods Regulations. An easier alternative (that does not require special transportation) is to send the stool sample surrounded by an ice pack that has been kept overnight in a -80°C freezer.

Stool samples are typically sent through the provincial public health laboratory, but samples can also be shipped directly to the NML using an NML shipping account; NML will cover the charges. To arrange this, contact the corresponding author by e-mail or telephone (204-789-6067). A requisition can be downloaded. It is most useful to include relevant clinical findings, travel and vaccination history, as well any relevant lab results that are available. Once samples arrive at the Enterovirus and Enteric Virus Section of the NML, multiple tests are done, including viral isolation in cell culture; typing of poliovirus isolates; screening for potential vaccine-derived polioviruses; and sequencing to confirm the presence of a wild-type, a Sabin-like or a vaccine-derived poliovirus strains. The total turnaround time is 28 days.

## An added benefit of AFP surveillance

Reporting and systematic stool testing of AFP cases in Canada can do more than document our polio-free status. Non-polio flaccid paralysis is frequently associated with non-polio enteroviruses (16), and these viruses can also cause encephalitis, meningitis and encephalomyelitis (17-19). For example, enterovirus A71 (EV-A71) has been causing periodic outbreaks of hand, foot and mouth disease in children, especially in Asia (20, 21). There are non-polio enteroviruses and novel syndromes that may be associated with emerging enteroviruses. Most non-polio enteroviruses affect children disproportionately, and some are potentially fatal.

An outbreak of enterovirus D68 (EV-D68) occurred in Canada and the United States in association with mostly mild respiratory illness in children (22-27). It has been suggested that acute flaccid myelitis (an unexplained neurological illness involving limb weakness in children) could be associated with EV-D68, since an increased incidence of these cases observed in the U.S. coincided with the increased detection of EV-D68 in 2014 (28).

These outbreaks underline the need to carry out continued and enhanced laboratory-based and epidemiological surveillance for AFP.

## Discussion

The global battle to eradicate the poliovirus is now at a critical point. The risk remains of the introduction of wild poliovirus and OPV-derived poliovirus in Canada and elsewhere from countries where it still is endemic. Due to this ongoing risk, vaccine coverage of the entire population and active surveillance of AFP in children less than 15 years of age continues to be critical.

Three things are essential to the eradication of polio: first, maintaining a high level of immunity in the population; second, ongoing vigilance, reporting and stool testing of all cases of AFP; and, third, accurate laboratory diagnostics to detect importations of poliovirus into Canada.

In addition to the need for better stool testing and reporting of AFP cases, this article identifies a gap in national polio surveillance activities. Currently, non-paralytic poliovirus infections in individuals who have not been recently vaccinated with OPV do not meet the national poliomyelitis case definition (29). As such, the list of poliovirus infections (**Appendix**) of which the Public Health Agency of Canada is aware of at this time may be incomplete. A review of provincial and territorial case definitions indicates that non-paralytic poliovirus infections are only notifiable in Ontario at this time (30). Given the emphasis on identifying and reporting all poliovirus infections, a revision to the national case definition to include such cases may be indicated.

Although many people believe the end of polio is now in sight, it may still take years of hard effort and vigilant surveillance before both wild PV1 and circulating OPV-derived polioviruses can finally be declared eradicated. Once eradication is achieved, there will be huge benefits in that the costs of continued global polio vaccination can eventually be saved and the infrastructure that was developed for polio eradication can then be devoted to addressing other health issues.

## Conclusion

The WHO's new vaccine recommendations and acute flaccid paralysis surveillance are both critical to eradicating polio. Canada's ongoing laboratory- and epidemiological-based polio surveillance is important for maintaining polio-free certification at a critical stage in world polio eradication. However, this can only happen with ongoing clinical vigilance for AFP that includes appropriate reporting and testing protocols.

## Acknowledgements

The authors wish to thank Susan Squires, Mary Louise Graham and Rukshanda Ahmad for their input on the clinical aspects of the paper and to Rhiannon Huzarewich, Lily MacDonald, Michelle Gusdal, Russel Mandes, Helen Bangura and Shelley Deeksfor their excellent technical assistance.

## Conflict of interest

None

## References

(1) World Health Organization (WHO). Polio Eradication & Endgame Strategic Plan 2013–2018. Geneva: WHO; 2013.
http://www.polioeradication.org/Portals/0/Document/Resources/StrategyWork/PEESP_EN_US.pdf

(2) World Health Organization (WHO). Statement on the 6th IHR Emergency Committee meeting regarding the international spread of wild poliovirus. Geneva: WHO; 2015 August 17.
http://www.who.int/mediacentre/news/statements/2014/polio-20140505/en

(3) Roberts L. Polio resurfaces in Mali and Ukraine. Science 8 September 2015. DOI: 10.1126/science.aad1723.
http://news.sciencemag.org/health/2015/09/polio-resurfaces-mali-and-ukraine

(4) van Regenmortel MHV, Fauquet CM, Bishop DHL, Carsten EB, Estes MK, Lemon SM, et al., editors. Virus Taxonomy: Seventh Report of the International Committee on Taxonomy of Viruses. San Diego, CA: Academic Press; 2000.

(5) Heymann DL, editor. Control of Communicable Diseases Manual. 20th ed. Washington, DC: American Public Health Association; 2014.

(6) Public Health Agency of Canada. Canadian Immunization Guide. Part 4—Active Vaccines: Poliomyelitis Vaccine [updated 2015 Feb 25]. http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-poli-eng.php

(7) Yakovenko ML, Gmyl AP, Ivanova OE, Eremeeva TP, Ivanov AP, Prostova MA, et al. The 2010 outbreak of poliomyelitis in Tajikistan: Epidemiology and lessons learnt. Euro Surveill. 2014 Feb 20;19(7):20706.

(8) Centers for Disease Control and Prevention (CDC). Progress toward interruption of wild poliovirus transmission—worldwide, January 2011–March 2012. MMWR 2012 May 18;61(19):353–7.

(9) Jafari H, Deshpande JM, Sutter RW, Bahl S, Verma H, Ahmad M, et al. Efficacy of inactivated poliovirus vaccine in India Science 22 August 2014: 345 (6199), 922-925. [DOI:10.1126/science.1255006]

(10) World Health Organization (WHO). Polio vaccines: WHO position paper, January 2014. Wkly Epidemiol Rec. 2014 Feb 28;89(9):73–92. http://www.who.int/wer/2014/wer8909.pdf?ua=1

(11) World Health Organization (WHO). Transmission of wild poliovirus type 2—apparent global interruption. Wkly Epidemiol Rec. 2001 Mar 30;76 (13): 95–7.

(12) Kew OM, Cochi SL, Jafari HS, Wassilak SGF, Mast EE, Diop OM, et al. Possible eradication of wild poliovirus type 3 —worldwide, 2012. MMWR. 2014 Nov 14;63(45):1031–3.

(13) Wassilak SG, Oberste MS, Tangermann RH, Diop OM, Jafari HS, Armstrong GL. Progress toward global interruption of wild poliovirus transmission, 2010–2013, and tackling the challenges to complete eradication. J Infect Dis. 2014 Nov; 210 Suppl 1:S5–15. doi:10.1093/infdis/jiu456.

(14) Canadian Paediatric Surveillance Program. Acute flaccid paralysis. http://www.cpsp.cps.ca/surveillance/study-etude/acute-flaccid-paralysis.

(15) Public Health Agency of Canada. Poliomyletis (Polio): Surveillance http://www.phac-aspc.gc.ca/im/vpd-mev/poliomyelitis/surveillance-eng.php

(16) Rao CD, Yergolkar P, Shankarappa KS. Antigenic diversity of enteroviruses associated with nonpolio acute flaccid paralysis. India, 2007–2009. Emerg Infect Dis. 2012 Nov;18(11). http://wwwnc.cdc.gov/eid/article/18/11/11-1457_article

(17) Rhoades RE, Tabor-Godwin JM, Tsueng G, Feuer R. Enterovirus infections of the central nervous system review. Virology. 2011 Mar 15;411(2):288–305. doi: 10.1016/j.virol.2010.12.014. Epub 2011 Jan 20.

(18) Lum LC, Wong KT, Lam SK, Chua KB, Goh AY, Lim WL, et al. Fatal enterovirus 71 encephalomyelitis. J Pediatr. 1998 Dec;133(6):795–8.

(19) Michos AG, Syriopoulou VP, Hadjichristodoulou C, Daikos GL, Lagona E, Douridas P, Mostrou G, Theodoridou M. Aseptic meningitis in children: Analysis of 506 cases. PLoS One. 2007 Aug 1; 2(7):e674.

(20) Wu W-H, Kuo T-C, Lin Y-T, Huang S-W, Liu H-F, Wang J, Chen Y-M A. Molecular epidemiology of enterovirus 71 infection in the central region of Taiwan from 2002 to 2012. PLoS One. 2013 Dec 31;8(12):e83711. doi: 10.1371/journal.pone.0083711.

(21) China on alert as virus spreads. BBC News. 2008 May 3. http://news.bbc.co.uk/2/hi/asia-pacific/7381741.stm

(22) Midgley CM, Jackson MA, Selvarangan R, Turabelidze G, Obringer E, Johnson D, et al. Severe respiratory illness associated with enterovirus D68—Missouri and Illinois, 2014. MMWR. 2014 Sep 12;63(36):798–9. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6336a4.htm

(23) Human enterovirus D68—North America (20): Update. ProMED. 2014 Dec 15. Archive No: 20141215.3035008. http://www.promedmail.org/direct.php?id=3035008

(24) Pastula DM, Aliabadi N, Haynes AK, Messacar K, Schreiner T, Maloney J, et al. Acute neurologic illness of unknown etiology in children—Colorado, August–September 2014. MMWR. 2014 Oct 10;63(40):901–2. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6340a5.htm

(25) Fonseca K, Kellner JD, Talbot J, Simmonds K, Anselmo M, Kuhn S, et al. Human enterovirus 68—Canada: (Alberta). Archive No. 20140916.2775534. 2014 Sep 16. http://www.promedmail.org/direct.php?id=2775534

(26) BC Centre for Disease Control. British Columbia Influenza Surveillance Bulletin. Influenza Season 2014–15, Number 9, Weeks 48–49, November 23 to December 6, 2014. 2014 Dec 11. http://www.bccdc.ca/NR/rdonlyres/35012AE9-2753-4A27-9DD5-87B3A11A40DC/0/InfluBulletin_Number09_Weeks4849_201415.pdf.

(27) Centers for Disease Control and Prevention. Enterovirus D68 in the United States, 2014. http://www.cdc.gov/non-polio-enterovirus/outbreaks/EV-D68-outbreaks.html

(28) Roos R., Center for Infectious Disease Research and Policy (CIDRAP). Link between polio-like illness and EV-D68 looks likely. CIDRAP News, 2014 Dec 2. http://www.cidrap.umn.edu/news-perspective/2014/12/cdc-link-between-polio-illness-and-ev-d68-looks-likely

(29) Public Health Agency of Canada. Case definitions for communicable diseases under national surveillance. Poliomyelitis. CCDR. 35S2. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/35s2/Polio-eng.php

(30) National Collaborating Centre for Infectious Diseases. Notifiable Disease Database. Accessed on July 24, 2014. http://nddb.ca/en/diseaseinfo/list

(31) Desai S, Diener T, Tan BJ-K, Lowry NJ, Talukdar C, Chrusch WM. An unusual case of vaccine-associated paralytic poliomyelitis. Can J Infect Dis Med Microbiol. 2014;25(4):227-8.

(32) Bartlett M, Murti M, Gubbay J, Khan A, Bontavics E, Simpson M, Booth T, Dolman S, Yaffe B, Chong-King E, Desai S, Finkelstein M. 9th Canadian Immunization Conference. Abstracts. Public health response to detection of poliovirus in Toronto. Can J Infect Dis Med Microbiol. 2010;21(4):14.

**Appendix: Identified poliovirus infections in Canada, 2004 to 2015[1]**

| Year | Virology test result | Symptoms | Source | Recent travel history | Outcome/ diagnosis |
|---|---|---|---|---|---|
| 2004[2] | Polio Sabin 1 | Diarrhoea | Stool culture | India | Incidental infection |
| 2005[2] | Polio Sabin 3 | Urinary tract infection | Stool culture | Unknown | Incidental infection |
| 2009 | Polio Sabin 3 | Acute flaccid paralysis | Stool culture | China | Probable case of vaccine-associated paralytic poliomyelitis (31) |
| 2009 | Polio Sabin 3 | Fever and cough | Nasopharyngeal culture | India | Incidental infection (32) |
| 2012[2] | Polio Sabin 2 | Diarrhoea | Stool culture | Philippines | Incidental infection |

[1]As of September 2015.
[2]Unpublished data.

Evaluation

# A spot of bother: Why varicella vaccine programs matter

**Harris T[1], Seo CY[1], Shing E[2], Wong K[1], Fediurek J[1], Deeks SL[1, 2]**

[1] Public Health Ontario, Toronto, ON
[2] Dalla Lana School of Public Health, University of Toronto, Toronto, ON

*Correspondence: tara.harris@oahpp.ca

## Abstract

**Objective:** To evaluate Ontario's provincial varicella vaccination program through analysis of aggregate varicella cases in order to determine whether there has been a decrease in reportable disease burden; and to assess varicella vaccine adverse events following immunization (AEFIs).

**Methods:** Aggregate varicella cases (1993–2013) were extracted from the reportable disease databases. Pre-program (1993–2004) and post-program (2007–2013) periods were chosen according to implementation of the publicly funded vaccination program. AEFIs following administration of varicella vaccines (2010–2013) were also extracted. Reporting rates were calculated using net doses distributed as the denominator. Serious AEFIs were defined using World Health Organization standards.

**Results:** The incidence of aggregate varicella reports decreased significantly over the study period (from 311.4 to 22.2 cases per 100,000 population in 1993 and 2013, respectively). Incidence also decreased significantly in all age groups between the pre- and the post-program periods with a shift in age distribution towards older individuals in the post-program period. A total of 162 AEFIs following varicella vaccine were reported between 2010 and 2013 for an annualized reporting rate of 14.6 per 100,000 doses distributed. The most common events were rash (37.3%), including eight reports of varicella-like rash (0.7 per 100,000 doses distributed). Ten serious events were reported (0.9 per 100,000 doses distributed), and all vaccine recipients recovered.

**Conclusion:** Significant reductions in varicella disease incidence and low AEFI reporting rates were observed with the introduction of the publicly funded varicella vaccine program in Ontario. Continued surveillance is indicated to further assess trends in varicella disease and vaccine safety.

## Introduction

Varicella, commonly known as chickenpox, is a primary infection caused by the varicella-zoster virus (VZV). Prior to the introduction of varicella vaccines, chickenpox was considered a ubiquitous disease of childhood affecting 90% of children by 12 years of age (1). Before varicella vaccines were available in Canada, approximately 350,000 varicella cases occurred each year with over 1,550 hospitalizations annually for all ages between 1994 and 2000 (1). In addition, 59 varicella-related deaths were reported throughout the country between 1987 and 1997 (1).

Live, attenuated varicella vaccine was first authorized for use in Canada in 1998, and was available for private purchase in Ontario (2). In September 2004, a single dose of varicella vaccine (Varilrix® [GlaxoSmithKline–GSK] or Varivax® III [Merck]) was added to Ontario's publicly funded immunization schedule for children 15 months of age. In August 2011, a second dose was added to the provincial schedule, administered as measles-mumps-rubella-varicella (MMRV) vaccine (Priorix-Tetra® [GSK]) at 4 to 6 years of age (3). In addition, children born on or after January 1, 2000, who were at least 1 year of age

were eligible for a second dose of varicella vaccine (4). One-dose varicella vaccine coverage was 77.8% among 5-year-olds in Ontario based on coverage assessment of school pupils for the 2012–2013 school year (5).

With the implementation of universal childhood varicella immunization programs, a decrease in disease incidence and varicella-related hospitalizations has been observed in Canada (6–10) and the United States (11–14). Decreases in varicella incidence and morbidity have also been observed in Australia and some European countries (e.g., Germany; parts of Italy and Spain) after the implementation of varicella vaccination programs (15–17). Extensive post-marketing surveillance of varicella vaccine safety over almost two decades has demonstrated an excellent safety profile where the majority of reported events are mild, including fever, rash and injection site reactions, and serious events are rare (18–21).

Assessment of immunization coverage, disease surveillance and vaccine safety data are essential components of comprehensive immunization program evaluation. Our objective is to evaluate the provincial varicella vaccination program through the analysis of aggregate reports of varicella cases throughout the period of program implementation, from 1993 to 2013; and the assessment of adverse events reported following administration of varicella-containing vaccines administered in Ontario between 2010 and 2013.

## Methods

In Ontario, reporting of varicella and adverse events following immunization (AEFIs) to the local medical officer of health is mandated by provincial public health legislation. Local public health units (PHUs) investigate reports and enter information according to provincial surveillance guidelines into the integrated Public Health Information System (iPHIS), the electronic reporting system for reportable diseases and AEFIs in Ontario. Varicella is reported as both individual cases and in aggregate numbers in iPHIS. All PHUs are required to report monthly aggregate counts by predefined age groups, as well as individually reporting cases that are laboratory-confirmed, hospitalized or have specified complications, including death (22, 23). Aggregate cases do not contain individual-level case details; they contain only information on age group, PHU, year and month of reporting. Herpes zoster is not a reportable disease in Ontario.

### Aggregate varicella reporting

Our analyses were limited to aggregate cases of varicella reported between January 1993 and December 2013. Individually reported cases of varicella were not included in the study. We extracted aggregate cases reported between 1993 and 2004 from the Ontario Public Health Portal on May 24, 2012, and aggregate cases reported between 2007 and 2013 from iPHIS on July 16, 2014. We excluded cases from 2005 and 2006 due to data completeness issues arising from transition in Ontario's reportable disease databases (from the Reportable Disease Information System to iPHIS). We selected pre- (1993–2004) and post- (2007–2013) publicly funded program periods based on the dates of implementation of the publicly funded varicella vaccination program in Ontario. The pre-program period includes time when varicella vaccine was available for private purchase, but not publicly funded (excluding the last four months of 2004). Incidence rate ratios (IRRs) were calculated to examine the changes in disease incidence between the two periods (i.e., the incidence rate in the post-program period divided by the incidence rate in the pre-program period). Trends in incidence rate over the entire study period were assessed using Poisson regression.

### Adverse events following immunization

On April 28, 2014, we extracted from iPHIS all AEFIs reported following administration of varicella-containing vaccines (monovalent varicella vaccines and MMRV vaccine) between January 1, 2010, and December 31, 2013. Descriptive analyses were limited to "confirmed" AEFIs which are defined as events that follow immunization which cannot be attributed to other causes. A causal relationship with the vaccine does not need to be proven.

Each AEFI report represents one vaccine recipient and one or more adverse events temporally associated with receipt of one or more vaccines. Adverse events were grouped by provincial case definitions. We selected age categories for analysis based on the recommended routine varicella immunization schedule (3). Reporting rates are calculated using net doses distributed within the publicly funded program as the

denominator. We defined serious AEFIs using the Public Health Agency of Canada AEFI reporting guidelines which are based on the World Health Organization standard definition (25,26). We conducted a key-word search of narrative case notes to identify varicella- or zoster-like rashes. Monovalent varicella and MMRV vaccine AEFIs are presented separately.

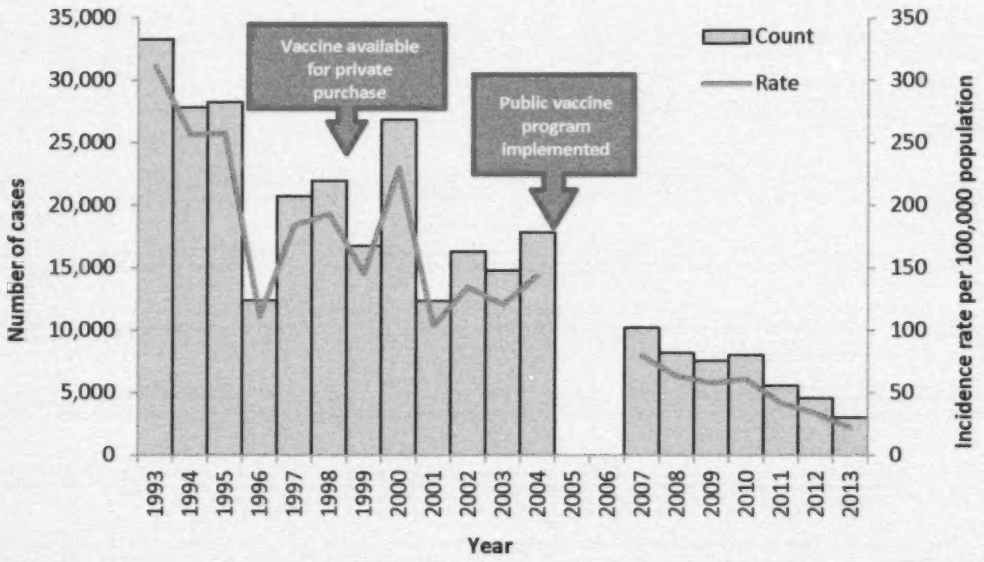
We performed statistical analyses using SAS (Statistical Analysis System) version 9.3 and Microsoft Excel 2010; p-values less than 0.05 were considered statistically significant.

## Results

### Aggregate varicella reporting

Between January 1993 and December 2013, a total of 295,928 aggregate varicella cases were reported in Ontario. Varicella incidence decreased significantly over the study period from 311.4 cases per 100,000 population in 1993 to 22.2 cases per 100,000 population in 2013 (**Figure 1**).

**Figure 1: Number of aggregate varicella cases and incidence in Ontario, 1993–2013 (n=295,928)**




Between the pre- and post-program periods, the overall incidence of varicella decreased from 180.5 to 51.0 cases per 100,000 population, for an IRR of 0.28 [95% confidence interval (CI): 0.28–0.29]. There was also a decrease in age-specific incidence which was significant in all age groups. The largest decline was observed in children in the 1- to 4-year-old age group, followed by the 5- to 9- and less than 1-year-old age groups (**Table 1**). In terms of age distribution, the 5- to 9-year-old age group continued to have the highest proportion of total varicella cases (57% in both periods); however, a shift in distribution towards older individuals was noted in the post-program period. Between the two periods, the proportion of cases among the 10- to 14-year-olds increased from 10.8% to 19.8%, while the proportion among the 1- to 4-year-olds decreased from 26.1% to 15.8%.

Table 1: Varicella incidence rate ratios comparing the pre-program period to the post-program period, by age group in Ontario, 1993–2013

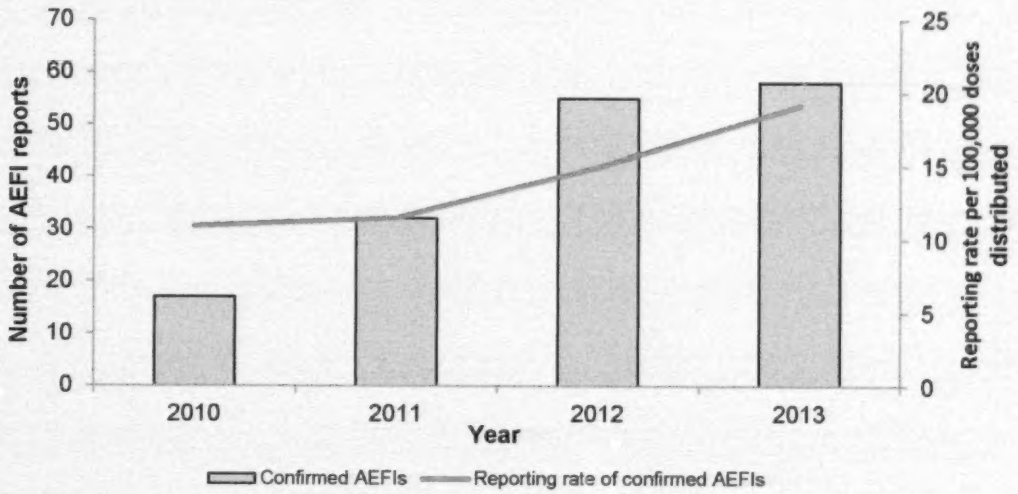
| Age group (years) | Pre-program incidence (per 100,000 population) | Post-program incidence (per 100,000 population) | Incidence rate ratio (95% confidence interval) |
|---|---|---|---|
| **Overall** | **180.5** | **51.0** | **0.28 (0.28–0.29)** |
| **<1** | 137.1 | 50.3 | 0.37 (0.33–0.40) |
| **01–04** | 899.9 | 183.9 | 0.20 (0.20–0.21) |
| **05–09** | 1,506.3 | 520.6 | 0.35 (0.34–0.35) |
| **10–14** | 282.0 | 167.6 | 0.59 (0.58–0.61) |
| **15–19** | 58.1 | 21.2 | 0.36 (0.34–0.39) |
| **≥20** | 6.5 | 2.7 | 0.41 (0.39–0.43) |

## Adverse events following immunization

### Monovalent varicella vaccine AEFIs

There were 162 confirmed AEFIs reported following administration of monovalent varicella vaccine and 1,106,143 doses of varicella vaccine distributed between January 1, 2010, and December 31, 2013. The annualized reporting rate was 14.6 per 100,000 doses distributed, and steadily increased from 10.9 per 100,000 doses distributed in 2010 to 19.1 per 100,000 doses distributed in 2013 (**Figure 2**). The age range was from 9 months to 70 years (median: 4.5 years); 38.9% of reports occurred in children between 12 and 23 months of age. Overall, 52.5% of AEFI reports were female; however, among adults over 18 years, 92.9% (n=13) were female.

Figure 2: Number of AEFIs reported following administration of monovalent varicella vaccines and reporting rate per 100,000 doses distributed in Ontario, by year, 2010–2013




Monovalent varicella vaccines were administered alone in 62.3% (n=101) of reports. Rash was the most commonly reported event (37.3%), followed by pain, redness or swelling at the injection site (32.9%) (**Table 2**). Key-word searching of case notes identified eight reports that described varicella-like rashes—all following the first dose of vaccine with a median time to onset of 7.5 days (range: 2 to 17 days). Seven of

these events occurred in children between 12 and 23 months of age and one occurred in an adolescent; none were laboratory-confirmed. There was also one report of laboratory-confirmed herpes zoster infection in a toddler with zoster-like symptoms 6.5 months after the first dose of vaccine. Genotyping confirmed vaccine-strain varicella zoster virus isolated from a skin specimen.

**Table 2: Number and distribution of varicella vaccine AEFIs in Ontario, by adverse event category, 2010–2013**

| Adverse event category[1] | Adverse event[2] | All AEFI reports n (%)[3] | Serious AEFIs n (%)[4] | Reporting rate (per 100,000 doses distributed) | Serious reporting rate (per 100,000 doses distributed) |
|---|---|---|---|---|---|
| **Allergic events** | **Total** | **37 (23.0)** | **2 (5.4)** | **3.3** | **0.2** |
| | • Allergic reaction—other | 2 (1.2) | 0 (0.0) | 0.2 | 0 |
| | • Allergic reaction—skin | 33 (20.5) | 1 (3.0) | 3.0 | 0.1 |
| | • Event managed as anaphylaxis | 2 (1.2) | 1 (50) | 0.2 | 0.1 |
| **Injection site reactions** | **Total** | **76 (47.2)** | **2 (2.6)** | **6.9** | **0.2** |
| | • Cellulitis | 18 (11.2) | 2 (11.1) | 1.6 | 0.2 |
| | • Infected abscess | 1 (0.6) | 0 (0.0) | 0.1 | 0 |
| | • Sterile abscess | 1 (0.6) | 0 (0.0) | 0.1 | 0 |
| | • Nodule | 10 (6.2) | 0 (0.0) | 0.9 | 0 |
| | • Pain/redness/swelling | 53 (32.9) | 0 (0.0) | 4.8 | 0 |
| **Neurologic events** | **Total** | **6 (3.7)** | **4 (66.7)** | **0.5** | **0.4** |
| | • Convulsions/seizures | 5 (3.1) | 3 (60.0) | 0.5 | 0.3 |
| | • Encephalopathy/encephalitis | 1 (0.6) | 1 (100.0) | 0.1 | 0.1 |
| **Other events of interest** | **Total** | **14 (8.7)** | **1 (7.1)** | **1.3** | **0.1** |
| | • Arthritis/arthralgia | 1 (0.6) | 0 (0.0) | 0.1 | 0 |
| | • Syncope with injury | 1 (0.6) | 0 (0.0) | 0.1 | 0 |
| | • Other severe/unusual events | 12 (7.5) | 1 (8.3) | 1.1 | 0.1 |
| **Systemic events** | **Total** | **69 (42.9)** | **5 (7.2)** | **6.2** | **0.5** |
| | • Fever ≥38°C | 18 (11.2) | 4 (22.2) | 1.6 | 0.4 |
| | • Persistent crying/screaming | 1 (0.6) | 0 (0.0) | 0.1 | 0 |
| | • Rash | 60 (37.3) | 1 (1.7) | 5.4 | 0.1 |
| | • Severe vomiting/diarrhea | 2 (1.2) | 1 (50.0) | 0.2 | 0.1 |

[1]Adverse event categories represent groupings of specific types of adverse events and are not mutually exclusive. For category totals, reports with more than one specific event within a category are counted only once. Thus category totals will not be the sum to the total of specific adverse events overall or within a category.
[2]Includes only those adverse events where the count was at least one.
[3]Each AEFI report may contain one or more specific adverse events which are not mutually exclusive. Percentages will not sum to 100%. The denominator of 162 is the total number of confirmed varicella AEFI reports between 2010 and 2013. The specific type of adverse event was missing for one report in 2011, and thus was excluded from the total confirmed AEFI reports in this specific analysis (n=161).
[4]Percent of reports that were serious within each event.

### MMRV vaccine AEFIs

There were eight confirmed AEFI reports following MMRV vaccine administered between August 8, 2011, and December 31, 2013. The reporting rate was 8.7 per 100,000 doses distributed. The median age was 5 years (range: 1 to 10 years). MMRV vaccine was administered alone in four of the eight reports. The most common events were injection site reactions (n=4) and allergic reactions (n=2) (including one anaphylaxis); none were serious.

## Discussion

This analysis found a significant reduction in varicella disease incidence at a population level and a low AEFI reporting rate following the introduction of the publicly funded varicella vaccine program in Ontario.

### Aggregate varicella reporting

Aggregate reporting of varicella was valuable in describing the overall trends in the epidemiology of disease in Ontario, despite data limitations described further below. The significant decrease in varicella incidence over the study period is consistent with findings observed in the U.S. (27, 28), and suggests that the publicly funded immunization program has had a positive impact on reducing varicella disease incidence in Ontario. This is further demonstrated by comparing the pre- and post-program periods, where the incidence was over three and a half times higher in the pre-program period than in the post-program period. It should also be noted that the pre-program period includes the years when the varicella vaccine was available for private purchase in Canada (1998–2004) which is a conservative measure as it would minimize the magnitude of decrease in disease incidence between the pre- and the post-program periods if a decrease in disease burden occurred as a result of private vaccine availability. Although the trends in varicella-associated health care utilization were out of scope for this analysis, the decrease in disease incidence mirrors the trends in decreasing varicella-associated hospitalizations observed in Canadian provinces, including Ontario (7–9). Furthermore, the declining incidence observed across all age groups, including those not targeted by the publicly funded immunization program (i.e., infants under 1 year of age), suggests a herd effect.

We would expect that a toddler vaccination program would change the age distribution of disease by shifting the burden of disease towards older individuals. In both the pre- and post-program periods, the majority of the varicella cases were observed among the 5- to 9-year-old age group. However, in the post-program period, more cases were reported in the 10- to 14-year-old age group than in the 1- to 4-year-old age group, in contrast to what was observed in the pre-program period. We may continue to see this shift in age distribution in the future as both the vaccinated cohort and the population with naturally-acquired immunity age, and as varicella vaccine coverage of the younger cohort increases. The significant decrease in varicella incidence since the implementation of the two-dose program in 2011 warrants further consideration on future requirements for varicella reporting in Ontario.

### Reported adverse events following immunization

AEFIs reported following varicella-containing vaccines administered in Ontario between 2010 and 2013 were consistent with the safety profile of varicella vaccines with no identification of any safety signals. The overall reporting rate of AEFIs following varicella vaccine (14.6 per 100,000 doses distributed) was comparable to reporting rates following other childhood vaccines administered in the second year of life in Ontario (29); however, it is lower than the AEFI reporting rates for varicella vaccine from the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) (74.0 per 100,000 doses distributed) (30), as well as passive AEFI surveillance systems in the U.S. and Europe (30.0 and 52.7 per 100,000 doses distributed, respectively) (19,20). The increase in the number of AEFI reports between 2010 and 2013 was anticipated given the expansion of the varicella immunization program in 2011.

Reported events were mostly mild (e.g., injection site reactions) and, as expected, rash was the most commonly reported event (37.3% of reports) which is consistent with observations from the U.S. and Europe (32.6% and 25.7%, respectively) (19, 20). Among all rashes, we identified a subset as varicella-like (vesicular) rash through key-word searching, although it is not clear if these were due to wild-type or vaccine strain as none were laboratory-confirmed. In addition, we identified a single report of laboratory-confirmed

vaccine-strain herpes zoster, an event which, while rare, has consistently been noted in post-marketing surveillance reports (18–21). Serious AEFI reports were infrequently reported and were generally related to known, but rare, reactions to varicella vaccine, including cerebellar ataxia, which has been reported following both wild-type varicella infection and after varicella vaccine administration (18-21, 31). The reporting rate of cerebellar ataxia following varicella vaccine was low (0.18 per 100,000 doses distributed), and similar to the rates from other post-marketing surveillance systems (18-20). No new or previously unknown serious events were reported.

Findings on MMRV vaccine are limited due to the low distribution of MMRV vaccine in the publicly funded program to date. As the use of this vaccine increases, an increase in AEFI reporting is expected and will contribute towards further understanding of the safety profile of this vaccine in Ontario.

### Limitations

Some limitations are inherent to many passive surveillance systems, including missing/incomplete data, reporting bias and under-reporting. In addition, the scope of this analysis is limited to only two out of three components of a comprehensive immunization program evaluation.

In terms of aggregate varicella reporting, under-reporting due to failure to report at the parent, physician, and/or PHU level would underestimate the burden of varicella in Ontario; however, the degree of under-reporting is not known. Additionally, because cases reported in aggregate cannot be reconciled with individual-level data (e.g., laboratory results, immunization data), data may include misclassified cases and some duplicate cases reported from more than one source. However, it is difficult to estimate the significance of duplicates and case misclassification without individual-level data.

For AEFI surveillance data, there was limited comparison to baseline rates, limited temporal trend analysis and lack of a population-based immunization registry. In addition, it has been noted elsewhere (29) that Ontario's overall AEFI reporting rate is less than half the national AEFI reporting rate, which is likely related to some degree of under-reporting as well as differences in AEFI reporting requirements in Ontario compared with other jurisdictions. With respect to varicella vaccine, pre-vaccination counselling about expected events following vaccine may also result in under-reporting of mild reactions specifically (i.e., fever, rash, injection site reactions), some of which are reportable as AEFIs in Ontario.

## Conclusion

Varicella disease incidence was significantly reduced following the introduction of the publicly funded varicella vaccine program in Ontario and no safety signals were identified. These findings contribute towards varicella immunization program evaluation in Ontario which is essential to ensure the continued success of the program. Surveillance is ongoing to further assess trends in varicella disease and AEFI reporting in the context of the recent change from a one- to a two-dose schedule.

## Acknowledgements

We would like to extend our sincere thanks to public health unit staff across the province for their efforts in investigation and reporting of varicella and adverse events following immunization which are essential to the assessment of the publicly funded program and vaccine safety in Ontario.

## Conflict of interest

None

## Funding

Funding for this project was provided by Public Health Ontario.

## References


(1) Public Health Agency of Canada. Varicella (Chickenpox). Ottawa, ON: Government of Canada; 2012 [updated 2012 Jul 23]. http://www.phac-aspc.gc.ca/im/vpd-mev/varicella-eng.php

(2) National Advisory Committee on Immunization. Varicella vaccination two-dose recommendations. CCDR. 2010;36(ACS-8):1–26.

(3) Publicly Funded Immunization Schedules for Ontario—August 2011. Toronto, ON: Queen's Printer for Ontario; 2011 [updated 2011 Aug 1;]. http://www.health.gov.on.ca/en/public/programs/immunization/docs/schedule.pdf

(4) Publicly Funded Immunication Schedules for Ontario—August 2011. Questions and Answers for Health Care Providers. Toronto, ON: Ministry of Health and Long-Term Care [updated 2011 Aug 10]. http://www.health.gov.on.ca/en/pro/programs/immunization/docs/qa_schedule.pdf

(5) Ontario Agency for Health Protection and Promotion (Public Health Ontario). Immunization coverage report for school pupils: 2012–13 school year. Toronto, ON: Queen's Printer for Ontario; 2014.

(6) Russell ML, Svenson LW, Yiannakoulias N, Schopflocher DP, Virani SN, Grimsrud K. The changing epidemiology of chickenpox in Alberta. Vaccine. 2005 Nov 16;23(46–47):5398–403.

(7) Kwong JC, Tanuseputro P, Zagorski B, Moineddin R, Chan KJ. Impact of varicella vaccination on health care outcomes in Ontario, Canada: Effect of a publicly funded program? Vaccine. 2008 Nov 5;26(47):6006–12.

(8) Fardeau de la varicelle et du zona au Québec,1990–2008 : impact du programme universel de vaccination. Québec, QC: Institut national de santé publique du Québec, Gouvernement du Québec; 2011 Apr. https://www.inspq.qc.ca/pdf/publications/1355_FardeauVaricelleZona1900-2008ImpactUnivVaccin.pdf

(9) Tan B, Bettinger J, McConnell A, Scheifele D, Halperin S, Vaudry W, et al. The effect of funded varicella immunization programs on varicella-related hospitalizations in IMPACT centers, Canada, 2000–2008. Pediatr Infect Dis J. 2012 Sep;31(9):956–63.

(10) Waye A, Jacobs P, Tan B. The imact of the universal infant varicella immunization strategy on Canadian varicella-related hospitalization rates. Vaccine. 2013 Oct 1;31(42):4744–8.

(11) Seward JF, Watson BM, Peterson CL, Mascola L, Pelosi JW, Zhang JX, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995–2000. JAMA. 2002 Feb 6;287(5):606–11.

(12) Reynolds MA, Watson BM, Plott-Adams KK, Jumaan AO, Galil K, Maupin TJ, et al. Epidemiology of varicella hospitalizations in the United States, 1995–2005. J Infect Dis. 2008 Mar 1;197 Suppl 2:S120–6.

(13) Guris D, Jumaan AO, Mascola L, Watson BM, Zhang JX, Chaves SS, et al. Changing varicella epidemiology in active surveillance sites—United States, 1995–2005. J Infect Dis. 2008 Mar 1;197 Suppl 2:S71–5.

(14) Chaves SS, Lopez AS, Watson TL, Civen R, Watson B, Mascola L, et al. Varicella in infants after implementation of the US varicella vaccination program. Pediatrics. 2011 Dec;128(6):1071–7.

(15) Khandaker G, Marshall H, Peadon E, Zurynski Y, Burgner D, Buttery J, et al. Congenital and neonatal varicella: Impact of the national varicella vaccination programme in Australia. Arch Dis Child. 2011 May;96(5):453–6.

(16) Carville KS, Riddell MA, Kelly HA. A decline in varicella but an uncertain impact on zoster following varicella vaccination in victoria, Australia. Vaccine. 2010 Mar 16;28(13):2532–8.

(17) European Centre for Disease Control and Prevention (ECDC). Varicella vaccine in the European Union. Stockholm, Sweden: ECDC; 2014 Apr. http://ecdc.europa.eu/en/publications/Publications/Varicella-guidance-2014-consultation.pdf

(18) Sharrar R, LaRussa P, Galea S, Steinberg S, Sweet A, Keatley R, et al. The postmarketing safety profile of varicella vaccine. Vaccine. 2000 Nov 22;19(7–8):916–23.

(19) Chaves SS, Haber P, Walton K, Wise RP, Izurieta HS, Schmid DS, et al. Safety of varicella vaccine after licensure in the United States: Experience from reports to the Vaccine Adverse Event Reporting System, 1995–2005. J Infect Dis. 2008 Mar 1;197 Suppl 2:S170–7.

(20) Goulleret N, Mauvisseau E, Essevaz-Roulet M, Quinlivan M, Breuer J. Safety profile of live varicella virus vaccine (Oka/Merck): Five-year results of the European Varicella Zoster Virus Identification Program (EU VZVIP). Vaccine. 2010 Aug 13;28(36):5878–82.

(21) Galea SA, Sweet A, Beninger P, Steinberg SP, Larussa PS, Gershon AA, et al. The safety profile of varicella vaccine: A 10-year review. J Infect Dis. 2008 Mar 1;197 Suppl 2:S165–9.

(22) Infectious Diseases Protocol. Appendix A: Disease-Specific Chapters. Chapter: Varicella (Chickenpox). Toronto, ON: Queen's Printer for Ontario; 2014 Jan. http://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/chickenpox_chapter.pdf

(23) Infectious Diseases Protocol. Appendix B: Provincial Case Definitions for Reportable Diseases. Disease: Varciella (Chickenpox). Toronto, ON: Queen's Printer for Ontario; 2014 Jan. http://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/chickenpox_cd.pdf

(24) Infectious Diseases Protocol. Appendix B: Provincial Case Definitions for Reportable Diseases. Disease: Adverse Events Following Immunization (AEFIs). Toronto, ON: Queen's Printer for Ontario; 2015 Apr http://www.health.gov.on.ca/en/pro/programs/publichealth/oph_standards/docs/aefi_cd.pdf

(25) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Post-Approval Safety Data Management: Definitions and

Standards for Expedited Reporting. E2D. Geneva: International Conference on Harmonisation; 2003 Nov 12. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf

(26) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. E2A. Geneva: International Conference on Harmonisation; 1994 Oct 27. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf

(27) Baxter R, Ray P, Tran TN, Black S, Shinefield HR, Coplan PM, et al. Long-term effectiveness of varicella vaccine: A 14-year, prospective cohort study. Pediatrics. 2013 May;131(5):e1389–96.

(28) Bialek SR, Perella D, Zhang J, Mascola L, Viner K, Jackson C, et al. Impact of a routine two-dose varicella vaccination program on varicella epidemiology. Pediatrics. 2013 Nov;132(5):e1134–40.

(29) Ontario Agency for Health Protection and Promotion (Public Health Ontario). Annual report on vaccine safety in Ontario, 2013. Toronto, ON: Queen's Printer for Ontario; 2015.

(30) Law BJ, Laflèche J, Ahmadipour N, Anyoti H. Canadian Adverse Events Following Immunization Surveillance System (CAEFISS): Annual report for vaccines administered in 2012. CCDR. 2014;40(S-3):7–23.

(31) Kuter B, Matthews H, Shinefield H, Black S, Dennehy P, Watson B, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. Pediatr Infect Dis J. 2004 Feb;23(2):132–7.

## ID News: Innovations in vaccine development and surveillance

Sifferlin A. **Scientists Unveil 'Promising First Step' to Universal Flu Vaccine.** Time. 2015 Aug http://time.com/4008699/universal-flu-vaccine-first-step/#4008699/universal-flu-vaccine-first-step/. *(Summary)*

Scientists are one step closer to developing a universal flu vaccine to protect against all strains of the virus. Researchers have known that the head of a viral protein called hemagglutinin changes easily, whereas its stem remains relatively unchanged. However, until now scientists have struggled to achieve an immune response with the stem rather than the ever-changing head. The researchers in the new study were able to formulate a vaccine that created antibodies from the stem. The vaccines showed success among a variety of lab animals...and protected against flu strains like H5N1 avian flu and H1N1 (swine flu).

Impagliazzo A, Milder F, Kuipers, Wagner M, Zhu X, Hoffman RMB, van Meersbergen R et al. **A stable trimeric influenza hemagglutinin stem as a broadly protective immunogen.** Science, Published Online 2015 Aug. doi: 10.1126/science.aac7263. *(Summary)*

The identification of human broadly neutralizing antibodies (bnAbs) targeting the hemagglutinin (HA) stem revitalized hopes of developing a universal influenza vaccine. Using a rational design and library approach, we engineered stable HA stem antigens ('mini-HAs') based on an H1 subtype sequence. Our most advanced candidate exhibits structural and bnAb binding properties comparable to full-length HA, completely protects mice in lethal heterologous and heterosubtypic challenge models, and reduces fever following sublethal challenge in cynomolgus monkeys. Antibodies elicited by this mini-HA in mice and nonhuman primates ... mediate antibody-dependent effector activity. These results provide proof-of-concept for design of HA stem mimics that elicit bnAbs against influenza A group 1 viruses.

**The American Association for the Advancement of Science: Onwards and Upwards.** The Economist. 2015 Feb. *(Summary)*

This year's meeting of the American Association for the Advancement of Science... devoted several sessions to the question of how vaccines can be made... and how the range of disease that can be vaccinated against might be extended... Jeffrey Ulmer (for example) described...Reverse vaccinology, as a child of genomics. It involves sequencing a bug's genetic material, using that knowledge to make lots of proteins that look like part of the target, and then screening these to see which provoke an immune response. Its most successful outcome so far is the creation of a vaccine, recently approved against meningococcus B... Dr. Ulmer also described a technique (that)...uses the body cells of a vaccinated individual to generate specially tailored antigens. RNA is a form of genetic material that a cell's protein-making machinery works with directly... Novartis researchers have exploited this by taking the RNA-replication machinery of a virus, removing the genes that let it make new viruses, and replacing them with RNA than encodes the antigen of interest. In effect, they have created a tiny antigen factory that will operate once it gets absorbed into a cell, vaccinating the individual in question as it does so.

Ulmer JB, Mansoura MK, Geall AJ. **Vaccines 'on demand': science fiction or a future reality.** Expert Opin Drug Discov. 2015 Feb;10(2):101-6. doi: 10.1517/17460441.2015.996128. Epub 2015 Jan 13. *(Summary)*

Self-amplifying mRNA vaccines are being developed as a platform technology with potential to be used for a broad range of targets. The synthetic production methods for their manufacture, combined with the modern tools of bioinformatics and synthetic biology, enable these vaccines to be produced rapidly from an electronic gene sequence. Preclinical proof of concept has so far been achieved for influenza, respiratory syncytial virus, rabies, Ebola, cytomegalovirus, human immunodeficiency virus and malaria.

Bettinger JA, Rouleau I, Gariépy MC, Bowie WR, Valiquette L, Vanderkooi OG, et al. on behalf of the Public Health Agency of Canada/Canadian Institutes for Health Research Influenza Research Network. **Successful methodology for large-scale surveillance of severe events following influenza vaccination in Canada, 2011 and 2012**. Euro Surveill. 2015;20(29):pii=21189. *(Summary)*

In 2011 and 2012, a nationwide Canadian vaccine safety surveillance network rapidly collected safety data from healthcare workers (HCW) during the first weeks of the annual influenza vaccination campaign... In 2012, these data were used to investigate a possible safety concern regarding a particular vaccine. An online questionnaire was provided to participating HCW two weeks before the annual influenza vaccination campaign for controls, and eight days after influenza vaccination for vaccinees. Control and vaccinees were requested to report health events occurring in the seven days prior to receiving the questionnaire. Control data were used to calculate background rates...More than 22,000 vaccinated HCW were enrolled and surveyed over two seasons and > 90% reported no severe event following vaccination. Validated severe event rates were similar in vaccinated HCW and unvaccinated HCW (2.2% vs 2.3%; $p < 0.70$)...Prior to the safety concern, the implicated vaccine was in use at one centre. Reassuring safety data were provided to public health authorities 48 hours after the vaccine was temporarily suspended. Data from this and similar networks can be used for rapid evaluation of vaccine safety.